REMARKS

This responds to the Office Action mailed on December 4, 2008.

Claims 1 and 43 are amended, claims 3-4, 33-42, 45-46, 61, and 63-64 are canceled and claim 65 is added. Claims 1-2, 5-7, 9-25, 27, 29-32, 43-44, 48-51, 53, 55-59, 62, and 65 are now pending in this application.

Claims 43 and 61 were objected to as the term "AAV" was not being concordant with the prior recitation of "enhance rAAV". The amendments to claim 43 and the cancellation of claim 61 address this objection.

The Examiner is kindly thanked for the courtesy of the telephonic interview on March 25, 2009, in which the rejections in the Office Action mailed on December 4, 2008 were discussed.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, 61-62, and 63-64 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate description and enablement. These rejections are respectfully traversed.

With regard to written description, the Examiner asserts that at issue are 1) the identify and structure of agents that enhance intracellular rAAV transduction in an amount effective to additively or synergistically enhance rAAV transduction; 2) the identity and structure of an agent that alters "uptake of rAAV at the cell membrane"; 3) the identity and structure of an agent that enhances "AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome"; and 4) whether a representative number of species has been described by their complete structure or sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus.

As amended, the claims are directed to the use of at least two different agents such as an anthracycline and a tripeptidyl aldehyde that inhibits proteosome proteolytic activity or epoxomicin, doxorubicin, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid and a tripeptidyl aldehyde that inhibits proteosome proteolytic activity.

With regard to agents that "alter cellular uptake of rAAV," see page 4 of the specification, which discloses that agents that alter cellular uptake of rAAV were known prior to Applicant's filing. Moreover, the specification discloses agents that enhance AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome, e.g., proteosome inhibitors and doxorubicin. Nevertheless, to advance the application, the claims no longer recite "an agent that alters uptake of rAAV at the cell membrane" or "an agent that enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome," thereby obviating bases 2) and 3) above for the written description rejection.

The specification discloses that agents useful to enhance AAV transduction are those that individually have different or overlapping activities (page 9). It is also disclosed that doxorubicin, an anthracycline, is an agent that may facilitate viral binding to proteosomes and/or subsequent transport into the nucleus (page 9). Other anthracyclines (see Example 8) also increased AAV transduction efficiency. Further, LLnL and Z-LLL are disclosed as agents that more significantly inhibit core proteolytic activity of proteosomes (page 9). Other proteosome inhibitors, at at least one of the three concentrations tested, increased AAV transduction efficiency (see Example 3 and Figure 1).

With regard to proteosome inhibitors, chemotherapeutics, such as anthracyclines, lipid lowering agents, such as simvastatin, antibiotics and tannic acid, those agents are known to the art. See, for instance, U.S. Patent No. 7,122,335, and the abstracts for Walsh et al. (Biochem. Soc. Trans., 31:487 (2003)), Phillips et al. (Curr. Op. Invest. Drugs, 3:1701 (2002)), Denny (Curr. Med. Chem., 9:1655 (2002)), Malhotra et al. (Cancer Biol. Ther., 2:52 (2003)), Backes et al. (Ann. Pharmacother., 39:523 (2005)), Davidson et al. (Prog. Cardiovasc. Dis., 47:73 (2004)), and Chung et al. (Crit. Rev. Food Sci. Nutr., 38:421 (1998)); a copy of each was enclosed with the Amendment filed on July 23, 2008. The Examiner has failed to address this evidence, as required by M.P.E.P. § 2163.04 (II). The Examiner is respectfully reminded that Applicant need not teach what is well known to the art, e.g., the structure of proteosome inhibitors, chemotherapeutics, such as anthracyclines, lipid lowering agents, such as simvastatin, antibiotics and tannic acid was known. Further, it is Applicant's position that those agents are generally known as having an activity that alters intracellular processes.

Moreover, WO 00/75365 (mentioned at page 59 of the application) discloses a structure for certain peptide-like compounds, lists other specific proteosome inhibitors and cites patents that disclose proteosome inhibitors that are useful to inhibit proteosome activity (that document is incorporated by reference at page 118 of the specification).

Thus, the claims recite relevant, identifying characteristics for the recited agents, i.e., each agent alone enhances intracellular rAAV transduction, and one agent is a chemotherapeutic such as an anthracycline, a lipid lowering agent, an antibiotic or a tannic acid, e.g., epoxomicin, doxorubicin, daunorubicin, idarubicin, epirubicin, aclarubicin, or simvastatin, and the other agent is a tripeptidyl aldehyde that inhibits proteosome core proteolytic activity, and those agents have a defined structure. Further, the specification discloses more than one species of anthracycline and more than one species of tripeptidyl aldehyde.

Therefore, the specification and claims satisfy the written description requirement of § 112(1).

The Examiner cites *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 U.S.P.Q.2d 1886, 1894-95 (Fed. Cir. 2004) to support the "written description" rejection. The case is not on point, however. The claims at issue in *Univ. of Rochester v. G.D. Searle & Co.* were claims to the use of an agent with a particular activity and, although the specification disclosed methods to identify an agent with the activity, the specification failed to disclose even a single agent with the recited activity. In contrast, Applicant's specification discloses more than one agent that enhances rAAV transduction, for instance, more than one anthracycline and more than one tripeptidyl aldehyde that enhances AAV transduction.

With regard to enablement, the Examiner asserts that because of the breadth of rAAV, mammalian cells and agents that alter distinct biologicially processes is large, the lack of correlation of cellular processes affected by each agent, and the limited teachings of co-administration of two or more agents altering biological processes so as to enhance AAV transduction from an enormous genus of mammalian cell types *in vitro* or *in vivo*, one of skill in the art would reasonably conclude that there is a high degree of unpredictability that any specific compound will enhance viral transduction or that any two agents will yield an additive interaction, and so it would require undue experimentation to practice the claimed invention.

It is Applicant's position that the preparation of a wide variety of rAAV is within the skill of the art and that a large number of different rAAV have been prepared (see, for instance, the abstracts for Sarkar et al., Blood, 103:1253 (2004); Arruda et al., Blood, 103:85 (2004); and Harding et al., Hum. Gene Thera., 17:807 (2006)) (a copy of each is enclosed herewith). Moreover, AAV has a broad host range (see Muzyczka, Curr. Top. Microbiol. Immunol., 58:97 (1992); a copy was enclosed with the Amendment filed on July 23, 2008; see also Denby et al. (Gene Ther., 12:1534 (2005)), Douar et al. (J. Virol., 75:1824 (2001)) and Jennings et al. (Mol. Ther., 11:600 (2005); a copy of each is enclosed herewith), i.e., AAV serotypes are known to infect many types of cells. In addition, the claims recite that each agent enhances AAV transduction and so excludes agents that do not enhance AAV transduction of particular cell types (see M.P.E.P. § 2164.08(b)). Further, the specification discloses the infection of HeLa cells, IB3 cells, A549 cells, ferret fibroblasts, mouse lung, trachea and bronchi, and airway epithelia with rAAV.

With regard to the *in vivo* use of rAAV and the recited agents, the Examiner is requested to reconsider that rAAV has been employed *in vivo* (see Duan et al., J. Clin. Investig., 105:1573 (2000)), and the abstract for Wu et al. (Vision Res., 48:1648 (2008)), Chen et al. (Pathol. Oncol. Res., epub May 29, 2008)) and Hsu et al. (Pharm. Res., epub February 22, 2008)); a copy of each abstract was enclosed with the Amendment filed on July 23, 2008)), as have chemotherapeutics, lipid lowering agents, antibiotics and tannic acid (a food additive). The Examiner is also requested to consider that those documents disclose the administration of rAAV locally to the retina or respiratory tract, or via injection, such as intrahepatic or portal vein injection, of mice or rats. Hence, it is within the skill of the art to select routes of administration for both rAAV and agents useful to enhance AAV transduction in various cell types in mammals.

The Examiner has failed to address the documents submitted with the Amendment filed on July 23, 2008 in support of enablement, as required in M.P.E.P. § 2164.04.

The Examiner cites Duan et al. (*supra*) as showing that LLnL did not effect the transduction of skeletal or cardiac muscle by AAV, indicating that tissue-specific ubiquitination of capsid proteins interferes with rAAV-2 transduction.

In fact, at page 1586 Duan et al. state that, with regard to results in skeletal and cardiac muscles, the results "suggest that ubiquitination and endosomal processing barriers to rAAV-2

transduction are likely to be organ specific and could explain the organ-specific tropisms observed with this virus." As noted in the abstract for Arruda et al. (*supra*), AAV-1, AAV-5 and AAV-7 transduce murine skeletal muscle much more efficiently than AAV-2 (Duan et al. employed rAAV-2). Therefore, serotypes other than AAV-2 may be employed to transduce muscle cells.

The specification discloses classes of agents useful in the methods and so provides direction on the types of agents to be employed in the method. As discussed above, chemotherapeutics, lipid lowering agents, antibiotics, tannic acid, and inhibitors of the proteolytic activity of proteosomes are known. As also discussed above, the specification discloses particular agents at page 51, line 23-page 52, line 8 and page 86, lines 14-31 that may be employed in the methods of the invention. The specification thus provides adequate direction and guidance to the art worker (Wands factor 2). The specification also discloses working examples of agents that enhance rAAV transduction (Wands factor 3). In addition, the Examiner acknowledges that the level of skill in the art is high (Wands factor 6).

With regard to the alleged undue experimentation to identity combinations of agents that at least additively enhance rAAV transduction, the Examiner simply cannot reasonably contend that a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance, particularly in view of Applicant's disclosure of particular classes of molecules to be employed in the methods.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and/or screen combinations of agents falling within the scope of the claims to identify those agents that at least additively enhance AAV transduction. See also, Hybritech Inc. v.

Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a variety of agents, mammalian cells and rAAVs is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

Evidence that screening numerous compounds to detect the effect of the compound on virus infection or replication is within the skill of the art was provided in the abstracts for Cheng et al. (Antimicro. Agents Chemother., 48:2437 (2004)) and Dhanak et al. (J. Biol. Chem., 277:38344 (2002)) (a copy of each was enclosed with the Amendment filed on July 23, 2008, however, for the Examiner's convenience, a copy of each is included herewith).

The Examiner asserts that both Cheng et al. and Dhanak et al. are drawn to assaying a specific target enzyme activity, not cell biological process such as viral uptake and intracellular trafficking and so these references were not considered commensurate in scope to the instantly claimed invention, that is because they do not establish that the artisan would know what specific enzyme must be targeted to screen for compounds having the desired activity, e.g., enhancement or inhibition of a specific enzyme that would clearly result in the instantly claimed function(s).

What Cheng et al. and Dhanak et al. evidence is that it is within the skill of the art to screen a large number of compounds to identify ones with desirable activity. The activity does not need to be enzymatic in nature. For instance, rAAV expressing any readily detectable marker gene, e.g., GFP (nonenzyme-mediated detection) or luciferase (enzyme-mediated detection), can be employed to detect transduction efficiency. Thus, a library of anthracyclines or proteosome inhibitors, or combinations thereof, may be readily screened for whether or not those agents alone, or in combination additively or synergistically, enhance rAAV transduction. Such a screen does not require knowledge of the underlying cellular process that is altered by the agent(s).

The Examiner also asserts that the artisan would essentially have to experiment by trial and error to determine which compounds possess the desired activity alone, specifically enhance "intracellular rAAV transduction", alter "uptake of rAAV at the cell membrane", and enhance

"AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome," and then determine by trial and error each combinatorial permutation to identify which compound(s) is capable of performing the recited function(s) in combination with one or more other compounds.

As discussed above, page 4 of the specification discloses that agents that alter cellular uptake of rAAV were known prior to Applicant's filing and the specification discloses agents that enhance AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome, e.g., proteosome inhibitors and doxorubicin. Given that disclosure, it is within the skill of the art to select those agents for use in the methods of the invention, for instance, the use of an agent that alters cellular uptake of rAAV in combination with the two recited agents. However, to advance the application, the claims no longer recite "an agent that alters uptake of rAAV at the cell membrane" or "an agent that enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome."

With regard to agents that enhance AAV transduction, the examples in the specification disclose numerous agents that enhance AAV transduction. It is certainly within the skill of the art in view of Applicant's specification to test other agents, for instance, other functionally or structurally related agents, to determine whether they alone, or in combination with a different agent, enhance AAV transduction. Examples 5 and 6 in the specification provide methods to determine if agents alter intracellular AAV processing.

The Examiner further asserts that Applicant has failed to address the substantive issue, which is the combined use of at least two or more agents having distinctly different functional activities to achieve a desired effect via an at least additive, if not synergistic interaction.

The Examiner is respectfully reminded that if Applicant's invention is disclosed so that one of ordinary skill in the art can practice the claimed invention, even if the practice of the invention by the art worker includes routine screening or some experimentation, Applicant has complied with the requirements of 35 U.S.C. § 112, first paragraph. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976); Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982). Thus, the art worker in possession of Applicant's specification would be apprised that the use of

anthracyclines or epoxomicin or simvastatin in combination with tripeptidyl aldehydes may enhance rAAV transduction, because similar agents likely have similar activities. It is Applicant's position that determining which combinations of those agents that enhance rAAV transduction is not undue experimentation in an art where the level of skill is high. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

The Examiner asserts that Goncalves (Virology J., 2:43 (2005)) teach that the ordinary artisan does not understand rAAV intracellular trafficking while the process regulating AAV trafficking into the nucleus may not be fully understood, the specification discloses that agents that modulate that process may be useful in the claimed methods. It is Applicant's specification that provides the predictability that certain classes of agents when exogenously co-administered enhance AAV transduction and provides methods to determine whether an agent alters intracellular AAV processing. The fact that the detailed nature of AAV trafficking in a cell may not be fully elucidated is irrelevant to whether the specification enables agents that enhance intracellular AAV transduction.

Accordingly, the specification is enabling.

Therefore, withdrawal of the § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 1-2, 4-7, 9-23, 43-44, 46, 48-50, 61, and 63-64 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. (J. Clin Invest., 105:1573 (2000)) in view of Kiyomiya et al. (Cancer Res., 61:2467 (2001), Maitra et al. (Am. J. Physiol. Cell Physiol., 280:C1031 (2001) and Engelhardt (U.S. Patent No. 6,436,392). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Duan et al. disclose that the combined effects of EGTA and LLnL on AAV transduction might be due to reduced degradation of internalized virus and an increased rate of endocytosis, and that the combination enhanced the amount of virus internalized from apical surfaces (page 1583). As LLnL does not alter AAV binding to cell surfaces or internalization (page 1581), it is likely EGTA altered AAV binding to cell surfaces or internalization, i.e., EGTA is not an inhibitor of proteosome proteolytic activity in AAV infected cells. In addition, EGTA is not an anthracycline, epoxomicin, aclarubicin, simvastatin or tannic acid.

Kiyomiya et al. disclose a mechanism for the nuclear transport of adriamycin, which may involve binding of adriamycin to the 20S proteosomes. However, there is nothing in Kiyomiya et al. related to virus transduction and adriamycin.

Maitra et al. relate that a single dose of doxorubicin increased total cellular CFTR protein expression, surface CFTR protein expression and CFTR-associated chloride secretion in T84 epithelial cells, and increased mutant CFTR cell surface expression and chloride secretion in stably transfected MDCK cells. Maitra et al. note that while the concentration of doxorubicin used *in vitro* (0.25 μM) was about 20-fold lower than the LD_{50}, doxorubicin is unlikely to be useful in a clinical setting due to its cumulative systemic toxicity (page C1037). There is nothing in Maitra et al. related to virus transduction and doxorubicin.

The Examiner asserts that because Maitra et al. disclose that the concentration of doxorubicin used *in vitro* (0.25 μM) was about 20-fold lower than the LD_{50}, Maitra et al. suggests that one might be able to achieve these effects *in vivo* at a low dose, suggesting further optimization to avoid toxicity yet retain desired activity (pages 21 and 22 of the Office Action). The Examiner also asserts that the claims do not recite the amount of doxorubicin that is used *in vivo* to avoid cytotoxicity.

CFTR is a gene associated with cystic fibrosis, a chronic disease. Thus, chronic administration of doxorubicin to a patient with cystic fibrosis may result in the cumulative systemic toxicity mentioned in Maitra et al. In this regard, the Examiner is respectfully requested to consider the Rule 132 Declaration enclosed herewith, executed by two of the named co-inventors of the present application, Dr. John Engelhardt and Dr. Ziying Yan. In the Declaration, Drs. Engelhardt and Yan state that doxorubicin, which binds DNA, inhibits topoisomerase II, and is used to treat cancer, would likely not be selected for administration to treat patients without an imminently life-threatening disease (such as cancer) because of its associated cytotoxicity. Moreover, Drs. Engelhardt and Yan state that, as noted in Maitra et al., the use of doxorubicin in a clinical setting, e.g., to treat cystic fibrosis via altering CFTR expression, is counter indicated due to its cumulative systemic toxicity. They also state that the use of a toxic agent may compromise cell viability, thereby defeating the goal of enhanced transduction of cells with rAAV, e.g., a rAAV encoding a therapeutic gene product. Drs. Engelhardt and Yan further note that given that doxorubicin binds DNA, it might be expected

that AAV transduction is inhibited by doxorubicin because AAV is present as a double stranded DNA molecule in the nucleus.

Therefore, Maitra et al. teach away from the chronic use of doxorubicin.

It is disclosed in the '392 patent that rAAV vectors, each containing a promoter and an open reading frame between ITRs, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

The '392 patent is not concerned with administering agents that enhance AAV transduction.

The Examiner asserts that proteosome systems are known to modulate the intracellular processing of many foreign molecules, including viruses (page 17 of the Office Action). As this is a form of Official Notice, the Examiner is requested to provide a reference or affidavit in support of such an assertion, as required by M.P.E.P. § 2144.03.

The Examiner asserts that while none of Duan et al., Kiyomiya et al. or Maitra et al. teach the formulations of doxorubicin and LLnL to achieve an additive or synergistic enhancement of rAAV transduction, it is well within the skill of the ordinary artisan to vary the respective concentrations of agents as part of routine optimization so as to identify conditions that would result in additive or synergistic enhancement, as demonstrated by Duan et al.

None of the cited documents, however, discloses or suggests certain agents and particular classes of agents, or combinations of classes of agents, to employ together to enhance AAV transduction. Therefore, there would be no reason for one of skill in the art to optimize conditions to enhance AAV transduction using those agents or classes of agents.

The Examiner also asserts that while the cited prior art does not teach that doxorubicin may be used to enhance rAAV transduction, alone or in combination with LLnL, those of ordinary skill in the art would have a reasonable expectation that such an activity would

necessarily flow from doxorubicin's activity in the cell, as the proteosome protease inhibitor LLnL enhanced rAAV transduction.

Given the teaching in Duan et al. to employ EGTA with a proteosome inhibitor, i.e., agents that have different activities, one of skill in the art would not have a reasonable expectation that agents with overlapping activities or untested combinations of agents would enhance AAV transduction.

In addition, the Examiner cannot logically sustain the position that it is unpredictable that any specific compound will enhance viral transduction or that any two agents will yield an additive interaction (see the enablement rejection above) and that there is a reasonable expectation that an agent with a potentially similar activity would be useful in a method that employs a different agent.

The Examiner asserts that since Kiyomiya et al. teach that doxorubicin is a proteosome protease inhibitor, it would likely also enhance rAAV transduction as being another species of that disclosed in Duan et al. Based on the Examiner's reasoning, one of skill in the art would employ doxorubicin and EGTA to enhance AAV transduction, i.e., agents that alter different steps in AAV infection.

The Examiner also asserts that it is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose (as well as to use such a composition for that purpose, i.e., to inhibit proteosome protease activity).

Contrary to the Examiner's assertions, the agents disclosed in the prior art were not for the same purpose. That is, LLnL was employed to enhance AAV transduction in Duan et al., and doxorubicin was found to increase CFTR expression and secretion in Maitra et al.

The Examiner further asserts that it is not unexpected that a combination of agents such as those with purportedly the same target would at least additively enhance AAV transduction and that agents that likely interact with proteosomes may be competitors for binding the proteosome.

Applicant respectfully traverses this assertion as an improper conclusory statement. For instance, the use of twice the amount of an agent (it has the "same" target) does not necessarily

result in twice the effect (see paragraph 8 in the Rule 132 Declaration enclosed herewith pointing to data in Yan et al. (J. Virol., 78:2863 (2004)).

In the absence of Applicant's disclosure, there is nothing in the cited art that would provide one of skill in the art with a reason to select the recited agents to enhance AAV transduction (which unlike EGTA do not enhance AAV uptake at the cell membrane), particularly in view of Duan et al. which teach the use of an agent that alters AAV binding to cell surfaces or internalization and an agent that inhibits proteosome proteolytic activity or otherwise reduces degradation of internalized virus, nor would provie one of skill in the art with the expectation that the use of the recited agents would result in an additive or synergistic effect. Further, Maitra et al. teach away from the use of doxorubicin "in a clinical setting." Also, unlike Duan et al., where two agents that act at different steps in AAV transduction, the present methods employ agents that may act on the same intracellular molecule in an amount that at least additively alters AAV transduction.

In the Rule 132 Declaration enclosed herewith, Drs. Engelhardt and Yan aver that in the absence of data, it is not predictable what combinations of agents have any effect, let alone have an additive or synergistic effect, on AAV transduction. Drs. Engelhardt and Yan refer to data provided in the Declaration on the effect of three compounds, and combinations of those compounds, on rAAV-2 or rAAV-5 transduction of IB3, A549 and HeLa cells. They state that the data and Yan et al. (J. Virol., 78:2863 (2004)) demonstrate that agents that purportedly have the "same" target (the proteasome) can result in a synergistic effect on AAV transduction and that agents that have a common structure, e.g., anthracyclines or peptide-like molecules, alone or in combination, can enhance AAV transduction. They also state that the data evidence that not all combinations of agents that individually enhance AAV transduction yield a positive or synergistic effect and that some combinations in fact reduce AAV transduction efficiency. Therefore, Drs. Engelhardt and Yan conclude that is not predictable what combinations of agents have any effect, let alone a positive or synergistic effect, on AAV transduction.

Further, Drs. Engelhardt and Yan state that the data also support the proposition that individual agents likely modulate proteasome activity and AAV transduction through their own unique mechanisms, e.g., there are two different pathways or steps in intracellular AAV processing related to proteasomes that may be altered and result in a synergistic effect on AAV

transduction. They explain that when specific mechanisms overlap, then at least a positive effect on AAV transduction may be observed.

Accordingly, withdrawal of the rejection of claims 1-2, 5-7, 9-23, 43-44, and 48-50 under § 103 is respectfully requested.

Claim 62 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. in view of Kiyomiya et al., Maitra et al. and Engelhardt et al. and further in view of Voinea et al. (J. Cell. Mol. Med., 6:465 (2002). This rejection is respectfully traversed.

Claim 62 depends on claim 1, which is believed to be patentable for at least the reasons discussed above. It is believed that the addition of Voinea et al. does not remedy the deficiency of Duan et al., Kiyomiya et al., Maitra et al. and Engelhardt et al. as discussed above.

Therefore, withdrawal of the rejection of claim 62 under § 103 is respectfully requested.

Claim 24 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. in view of Kiyomiya et al., Maitra et al. and Engelhardt et al. and further in view of Hirsch et al. (U.S. Patent Application Publication No. 2003/0003583). This rejection is respectfully traversed.

Claim 24 depends on claim 1, which is believed to be patentable for at least the reasons discussed above. It is believed that the addition of Hirsch et al. does not remedy the deficiency of Duan et al., Kiyomiya et al., Maitra et al. and Engelhardt et al. as discussed above.

Thus, withdrawal of the rejection of claim 24 under § 103 is respectfully requested.

CONCLUSION

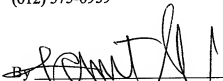
Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6959

Date May 4, 2009

By 
Janet E. Embretson
Reg. No. 39,665

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Zhakalazky M. Carrion
Name

Signature